

Molecular mechanism for some anti-arrhythmia drugs discovered

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University of British Columbia researchers – using an innovative, atom-by-atom substitution method – have uncovered the mechanism by which a particular class of drugs controls irregular heartbeats.

The findings, published today in the online journal *Nature Communications*, shed light on why certain anti-arrhythmic drugs (AADs) have dramatically different effects on the heart's behavior compared to others, and why the same [drug](#) can be beneficial in some instances and fatal in others. The discovery points the way toward development of better treatments for the condition, which is a leading cause of stroke.

AADs are typically categorized on the basis of their effects on the electrocardiogram (ECG), not on their inherent qualities or molecular mechanisms. Such sorting of drugs, while common in pharmacology, limits our ability to improve upon them, said principal investigator Chris Ahern, an Assistant Professor in the UBC Department of Anesthesiology, Pharmacology and Therapeutics.

"By understanding how these drugs work at the molecular level, we will be better able to pick and choose the traits we want – and those we don't – when developing new drugs for this dangerous condition," said Ahern, who is a member of the Life Sciences Institute at UBC and of the Brain Research Centre at UBC and the Vancouver Coastal Health Research Institute.

All three categories of Class 1 AADs, called Class 1a, 1b and 1c, bind to the same site within the cardiac sodium channel, a sophisticated protein that generates electrical impulses to the heart. Ahern, working with postdoctoral fellow Stephan Pless, in the same department, and Jason Galpin and Adam Frankel from the Faculty of Pharmaceutical Sciences, sought to discover whether the differences were due to varying levels of electrostatic interactions between the drugs and the [amino acids](#) in the channel.

They created artificial amino acids to mirror the behavior of the cardiac sodium channel, probing the AADs' structure and the contribution of electrical charge – a technique that follows in the footsteps of UBC Nobel Laureate Michael Smith and has been used successfully by a few labs worldwide. The researchers substituted individual hydrogen atoms with fluorine atoms, which display different electrical characteristics, to see if those modifications affect the AADs' ability to bind to the cardiac sodium channel.

The various alterations of the amino acids were introduced into cells, and the researchers measured the resulting electrical current. They found that each substitution of a hydrogen atom with a fluorine atom lowered the level of AAD binding to the cardiac sodium channel.

"We did this in steps, and observed a clear trend with the Class 1b AADs," said Pless, who has been working at UBC since 2008 on a research fellowship from the Heart & Stroke Foundation of BC & Yukon. "The trend held over each atom replacement, which confirmed that electrostatic reactions are indeed taking place with the drugs. But we found little evidence of the same electrical interaction with 1a and 1c drugs."

The distinction of 1b drugs explains their particular ability to both rapidly change the heart's behaviour, and to rapidly "shut off," Pless

said.

"By zeroing in on these molecular actions, drug developers will be better able to isolate the most desirable qualities of each drug – as well as the most threatening – to find a more effective, safer version," he said.

Provided by University of British Columbia

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